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- (71) Applicant: ZENTARIS AG [DE/DE]; Weismüllerstrasse 45, 60314 Frankfurt (DE).
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- (72) Inventors: ENGEL, Jürgen; Erlenweg 3, 63755 Alzenau (DE). VOGELI, Rainer; Am Berg 4, 63599 Biebergemünd-Bieber (DE).



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(54) Title: TREATMENT OF DEMENTIA AND NEURODEGENERATIVE DISEASES WITH INTERMEDIATE DOSES OF LHRH ANTAGONISTS

(57) Abstract: The present invention relates to the treatment of dementia and neurodegenerative diseases like Alzheimer's disease with intermediate doses of LHRH antagonists which do not cause a castration. A preferred LHRH antagonist is cetrorelix.

Treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists

The present invention relates to the treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists which do not cause a castration.

FURUYA, Shuichi et al. in WO 01/78780 teach preventives and remedies for Alzheimer's disease containing a compound having GnRH antagonism have effects of preventing and treating Alzheimer's disease with little toxicity.

It has been shown in a study by Bowen R.L et al. that serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were significantly higher in individuals suffering of dementia, e.g. Alzheimer's disease. Bowen R.L. et al. propose in their patent application CA 2,309,395 (US priority June 4, 1999, 09/326,180) to lower FSH and LH to minimal levels by the use of castrating doses of analogues of the LH-releasing hormone (LHRH), either super-agonists or antagonists.

This treatment would be accompanied by highly undesirable side effects as lowering sex hormone levels to castration levels would result in loss or reduction of libido, sexual desire and sexual potency. In men and pre-menopausal women this treatment would also result in the typical symptoms of drop of sex hormones like hot flushes, etc. Women would additionally suffer from loss of bone minerals that would limit the treatment.

These side effects could be reduced by hormone replacement therapy.

It has been found now that the treatment with intermediate doses of LHRH antagonists results in a sub-maximal lowering of FSH and LH to normal levels that leaves sex hormone levels above the castration threshold.

This treatment is highly advantageous as it gives the desired results of normalising FSH and LH levels without the undesirable side-effects of sex hormone blockade. Thus the additional treatment of sex hormone replacement becomes superfluous.

The present invention relates to the treatment of dementia and neurodegenerative diseases with intermediate doses of LHRH antagonists, wherein the antagonist is preferably cetrorelix, teverelix, antide or abarelix. The antagonist can also be the LHRH antagonist D-63 153 (Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH₂) as described in the PCT application WO 00/55190 A1.

The mentioned LHRH antagonists can also exhibit a heterocyclic skeletal structure. Such peptidomimetics can be for example

- 1-[7-Chloro-3-(3,5-dimethyl-phenyl)-2-oxo-4-(2-piperidin-2-yl-ethoxy)-1,2-dihydro-quinolin-6-yl]-3-pyridin-2-yl-urea (described in WO 97/44339),
- 3-[Benzyl-methyl-amino)-methyl]-2-*tert*-butyl-8-(2-fluoro-benzyl)-6-(3-methoxy-phenyl)-7-methyl-8*H*-imidazo[1,2-*a*]pyrimidin-5-one (described in WO 01/29044),
- 2-(2,5-Dimethyl-furan-3-yl)-8-(2-fluoro-benzyl)-3-([methyl-(2-pyridin-2-yl-ethyl)-amino]-methyl)-5-oxo-5,8-dihydro-imidazo[1,2-*a*]pyrimidine-6-carboxylic acid 1-ethyl-propylester (described in WO 00/69859),
- 3-((2-[2-(3,5-Difluoro-phenyl)-1-(2-methoxy-benzoyl)-2-oxo-ethylidene]-2,3-dihydro-1*H*-benzimidazol-5-yl-amino)-methyl)-benzonitrile (described in WO 02/02533).

The LHRH antagonist is given in a monthly dose of 10 to 100 mg per month and the treatment is repeated monthly, two-monthly or lasting several months.

In a preferred embodiment the LHRH antagonist is given in a monthly dose of 30 to 60 mg per month and the treatment is repeated monthly, two-monthly or lasting several months.

Pharmaceutical formulations of the LHRH antagonist suitable for the therapeutic management of dementia and neurodegenerative diseases may be for example

- a) acetate salt formulations of the active compounds in the concentration of 1 mg/1 ml or lower where the lyophilisate powder may be dissolved in water for injection or in gluconic acid;
- b) acetate salt formulations of the active compounds in the concentration of 1.5 mg/1 ml to 5.0 mg/1 ml, preferably 2.5 mg/1 ml where the lyophilisate powder may be dissolved in water for injection or in gluconic acid;
- c) pamoate salt formulations of the active compounds in the concentration of 10 mg/1 ml to 30 mg/1 ml, preferably 15 mg/1 ml where the lyophilisate powder may be dissolved in gluconic acid or in water for injection.

Suitable excipients and dosage forms are for example described by K.H. Bauer, K.-H. Frömming and C. Führer, Lehrbuch der Pharmazeutischen Technologie, 6th edition, Stuttgart 1999, pages 163-186 (excipients) and pages 227-386 (dosage forms), including the references as cited therein.

The LHRH antagonist can be administered for example subcutaneous, oral, intramuscular or inhalative.

The disease as mentioned, for example can be treated in accordance with the following scheme.

Example

In one embodiment of the invention a single dose of 30-60 mg of cetorelix is administered by injection per month. The treatment is continued monthly. In another embodiment the treatment is continued two-monthly or lasting several months after the administration of the single dose.

Claims

1. Use of a LHRH antagonist for the preparation of a medicament for the treatment of dementia and neurodegenerative diseases in humans by administration of intermediate doses, which do not cause a castration.
2. Use according to claim 1, characterized in that the monthly single dose is in the range of 10 – 100 mg LHRH antagonist.
3. Use according to claims 1 and 2, characterized in that the monthly single dose is about 30 to about 60 mg LHRH antagonist.
4. Use according to one of claims 1 to 3, characterized in that the administration is continued on a monthly or two-monthly or lasting several months base.
5. Use according to one of claims 1 to 4, characterized in that the treated disease is Alzheimer's disease.
6. Use according to one of claims 1 to 5, characterized in that the LHRH antagonist is cetrorelix.
7. Use according to one of claims 1 to 5, characterized in that the LHRH antagonist is teverelix.
8. Use according to one of claims 1 to 5, characterized in that the LHRH antagonist is antide.
9. Use according to one of claims 1 to 5, characterized in that the LHRH antagonist is abarelix.

10. Use according to one of claims 1 to 5, characterized in that the LHRH antagonist is D-63 153 (Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hcl-Nle-Arg-Pro-D-Ala-NH₂).
11. Use according to one of claims 1 to 5, characterized in that the LHRH antagonist is a peptidomimetic.
12. Use according to claim 11 in which the peptidomimetic is a compound
- 1-[7-Chloro-3-(3,5-dimethyl-phenyl)-2-oxo-4-(2-piperidin-2-yl-ethoxy)-1,2-dihydro-quinolin-6-yl]-3-pyridin-2-yl-urea
 - 3-[Benzyl-methyl-amino)-methyl]-2-*tert*-butyl-8-(2-fluoro-benzyl)-6-(3-methoxy-phenyl)-7-methyl-8*H*-imidazo[1,2-a]pyrimidin-5-one
 - 2-(2,5-Dimethyl-furan-3-yl)-8-(2-fluoro-benzyl)-3-([methyl-(2-pyridin-2-yl-ethyl)-amino]-methyl)-5-oxo-5,8-dihydro-imidazo[1,2-a]pyrimidine-6-carboxylic acid 1-ethyl-propylester or
 - 3-((2-[2-(3,5-Difluoro-phenyl)-1-(2-methoxy-benzoyl)-2-oxo-ethylidene]-2,3-dihydro-1*H*-benzimidazol-5-yl-amino)-methyl)-benzonitrile.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/09 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, CHEM ABS Data, BIOSIS, PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 309 395 A (BOWEN RICHARD LLOYD) 4 December 2000 (2000-12-04)	1
Y	page 10, line 10 - line 20 page 11, line 26 - page 12, line 10 page 12, line 15	1-12
Y	WO 00 55190 A (ASTA MEDICA AG) 21 September 2000 (2000-09-21) cited in the application claim 4	1-10
Y	WO 97 44339 A (GOULET MARK ;JIANG JINLONG (US); ALLEN ERIC E (US); DEVITA ROBERT) 27 November 1997 (1997-11-27) cited in the application example 1	1-12

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Z document member of the same patent family

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Giacobbe, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No

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